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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SLOBODYANSKY, ELIZABETH	
ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 11/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/974,973	HANKE, PAUL D.	
	Examiner	Art Unit	
	Elizabeth Slobodyansky, PhD	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-20 and 24-31* is/are pending in the application.

4a) Of the above claim(s) *9-11 and 14-18* is/are withdrawn from consideration.

5)☒ Claim(s) *2,3 and 25* is/are allowed.

6)☒ Claim(s) *1,5-8,12,13,19,20,24 and 26-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 August 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed August 25, 2004 amending the specification to clarify the text at paragraph [0010], amending claims 1, 2, 19 and 20 and adding claims 24-31 has been entered.

The statement regarding the biological Deposit of *E. coli* NRRL B-30293 is given in Remarks of August 25, 2004 (page 11).

Claims 1-3, 5-20 and 24-31 are pending. Claims 9-11 and 14-18 are withdrawn. Claims 1-3, 5-8, 12, 13, 19, 20 and 24-31 are under consideration.

Drawings

The corrected drawing of Figure 4 was received on August 25, 2004. This drawing is acceptable.

Claim Rejections - 35 USC 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19 and 20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 19 and 20 have been amended to recite a polypeptide or a nucleotide sequence, respectively, comprising all seven sequences of SEQ ID NOs: 6, 8, 10, 12, 14, 16 and 18, or SEQ ID NOs: 5, 7, 9, 11, 13, 15 and 17, as opposed to a previous version of the claims that recited a sequence selected from the group consisting of seven sequences. The Examiner is unable to locate adequate support in the specification for sequences comprising all seven sequences. Thus there is no indication that nucleic acid molecules comprising said sequences were within the scope of the invention as conceived by Applicants at the time the application was filed.

Accordingly, Applicants are required to cancel the new matter in the response to this Office Action.

Claims 1, 5-8, 12, 13, 19 and 20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a DNA encoding SEQ ID NO:2, including SEQ ID NO:1, a DNA encoding a pyruvate carboxylase having an amino acid sequence that differs from SEQ ID NO:19 by at least one of the seven specific mutations, said pyruvate carboxylase being desensitized to feedback inhibition by aspartic acid and a DNA at least 95 % identical to SEQ ID NO:1 encoding a pyruvate carboxylase having an amino acid sequence comprising all seven specified mutations in SEQ ID NO:19 said pyruvate carboxylase being desensitized to feedback inhibition by aspartic acid, does not reasonably provide enablement for a DNA at least 95% identical to SEQ ID NO:1 encoding a pyruvate carboxylase that is desensitized to feedback inhibition by aspartic acid, said mutant

pyruvate carboxylase having an amino acid sequence containing at least one of the seven specific mutations or comprising SEQ ID NOs:6, 8, 10, 12, 14, 16 and 18. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Factors pertinent to this discussion include predictability of the art, guidance in the specification, breadth of claims, and the amount of experimentation that would be necessary to use the invention.

Claim 1, with dependent claims 5-8, 12 and 13, is directed to a nucleic acid at least 95% identical to SEQ ID NO:1 encoding a pyruvate carboxylase that is desensitized to feedback inhibition by aspartic acid, said mutant pyruvate carboxylase having an amino acid sequence containing at least one mutation selected from the group consisting of seven specific mutations in SEQ ID NO:19.

The specification teaches a DNA of SEQ ID NO:1 that encodes a mutant pyruvate carboxylase of SEQ ID NO:2 having seven specific mutations relative to the

wild-type sequence of SEQ ID NO:19. The specification does not teach any DNA sequence at least 95% identical to SEQ ID NO:1 encoding a pyruvate carboxylase with the requisite property comprising only one of the seven specified mutations and additional mutations at any positions. The specification does not disclose which of the seven mutations if there is/are less than seven that are responsible for making the pyruvate carboxylase desensitized to feedback inhibition by aspartic acid. Further, it fails to provide information regarding other combinations of substitute amino acids that would result in a mutant with the requisite characteristics. The art discloses a DNA that encodes a pyruvate carboxylase having the amino acid sequence that differs from SEQ ID NO:19 by replacement of methionine at position 1 with a valine, said enzyme apparently not being feed-back resistant (Sinskey et al. Database Genseq, accession AAB01436, sequence alignment). Thus, it appears that at least mutation M1V in SEQ ID NO:19 does not impart the requisite function. While there is a great number of possible mutants, it is *a priori* unpredictable as to which mutant will exhibit the claimed property. Therefore, the breadth of these claims is much larger than the scope enabled by the specification. With regard to claims 19 and 20, SEQ ID NO: 6 is a fragment of SEQ ID NO:2 corresponding to residues 164-176. Therefore, SEQ ID NO: 6 (13 amino acids) comprises a single mutation at position corresponding to position 153 in SEQ ID NO: 19. SEQ ID NO: 18 is a fragment of SEQ ID NO:2 corresponding to residues 1-18. Therefore, SEQ ID NO: 18 comprises a single mutation at position corresponding to position 1 in SEQ ID NO: 19 that appears to be unimportant for the requisite function, *supra*. SEQ ID NOs: 8, 10, 12,

14 and 16 (13 amino acids each) comprise no mutations compared to SEQ ID NO:19.

The amino acid sequence of a protein determines its structural and functional properties, and predictability of what changes in the amino acid sequence can be tolerated and result in similar activity is extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's structure from mere sequence data are limited. Furthermore, while recombinant techniques are available, it is not routine in the art to screen large numbers of peptide mutants where the expectation of obtaining similar activity is unpredictable based on the instant disclosure.

The specification does not support the broad scope of the claims which encompass DNAs at least 95% identical to SEQ ID NO:1 encoding a pyruvate carboxylase with the requisite property comprising less than seven specified mutations and additional mutations at any positions because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting the requisite pyruvate carboxylase activity; (B) the general tolerance of said pyruvate carboxylase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any pyruvate carboxylase residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Therefore, one of ordinary skill would require guidance, such as information regarding the specific amino acid changes that would render a pyruvate carboxylase desensitized to feedback inhibition by aspartic acid, in order to make a DNA at least 95% identical to SEQ ID NO:1 encoding a mutant pyruvate carboxylase with the requisite property and comprising less than seven specified mutations in SEQ ID NO:19 in a manner reasonably correlated with the scope of the claims. Without such guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 24, with dependent claims 26-31, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 24 is unclear because it is not clear that the claimed sequence may have at least one of the seven specific mutations but not more than all seven specific mutations.

Claim 28 is unclear because it is drawn to "A method for producing a host cell comprising introducing the vector of claim 26 into a host cell". The claim does not distinguish between the starting and the resulting host cell. It is suggested to amend the claim to recite a method for producing a transformed cell comprising introducing the vector of claim 26 into a host cell, for example. For the same reason, the use of "a host cell" in claim 31 is confusing.

Allowable Subject Matter

Claims 2, 3 and 25 are allowed.

Response to Arguments

Applicant's arguments filed August 25, 2004 have been fully considered but they are not persuasive.

Applicant argues that "As discussed in Applicant's response of August 22, 2003, and set forth in references incorporated in the specification and provided in the Information Disclosure Statement filed on August 19, 2002 (Modak, H.V. and Kelly, D.J., Microbiology *141*:2619-2628 (1995), and Attwood, P.V., *Int. J. Biochem. Cell. Biol. 27*:231-249 (1995)), the structure of pyruvate carboxylase was known at the time that the invention was made.[2] Attwood at Figure 10, page 242, sets forth an amino acid sequence of pyruvate carboxylase in yeast, including amino acid residues responsible for binding and activity of the enzyme. Attwood goes on to describe a region conserved between yeast pyruvate and transcarboxylase, as well as sequence homology among various biotin carboxylases at the N-terminus, the biotinyl domain, which corresponds to the mutation identified in SEQ ID NO:16. Furthermore, as was previously noted, none of the mutations suggested in claim 1 are located in the region characterized by Attwood as required for pyruvate binding (Remarks, paragraph bridging pages 14-15). These arguments are not persuasive

because these references do not teach which residues are responsible for desensitization to feedback inhibition by aspartic acid. The specification does not teach whether less than all seven mutations can impart the requisite function. In other words the specification does not identify a single mutation or any less than all seven mutations that would result in a requisite property. There is no guidance as to what are other residues mutations of which would impart the requisite function.

While methods to produce variants of a known sequence such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan producing variants as claimed by applicants (i.e., encoding a mutant pyruvate carboxylase that is desensitized to feedback inhibition by aspartic acid) requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the infinite number of variants have the claimed property. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute **undue** experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has **not** been provided in the instant specification.

Applicant further argues that "the number of combinations of the seven mutations is not so great that an unreasonable amount of experimentation is necessary to successfully isolate a sequence of the invention" (page 15). It is agreed

that combinations of seven mutations is within reasonable amount of experimentation. That is why claim 24, if more clearly worded, will be allowable. It appears to be reasonable to find residues that would not affect the requisite property of mutated SEQ ID NO:19 comprising all seven mutations. However, to find combinations of mutations resulting in the requisite property other than the combination of all seven mutations is deemed as undue experimentation.

Applicant argues that "SEQ ID NOs: 6, 8, 10, 12, 14, 16, and 18 represent conserved portions of SEQID NO:2, at positions 164-176, 193-205,217-229, 238-250, 466-478, 1127-1139, and 1-18 of SEQ ID NO:2, respectively, and that satisfaction of claim 19 would include conservation of these sequences at similar relative locations in an amino acid sequence generated by a nucleotide sequence 95% identical to SEQ ID NO:1" (paragraph bridging page 15-16). This is not persuasive because only two of these sequences comprise the two of the mutations while other sequences comprise no mutations. The importance of their conservation for the requisite function is not disclosed in the specification or known in the art. These sequences together comprise 96 amino acids that represent only about 8% of SEQ ID NO:2 (1157 amino acids).

The previous 112, 2nd paragraph, rejection is withdrawn in view of the amendment.

The previous 102(a) rejection is withdrawn in view of the amendment.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky, PhD whose telephone number is 571-272-0941. The examiner can normally be reached on M-F 10:00 - 6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, PhD can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

E. Slobodyansky

Elizabeth Slobodyansky, PhD